Fractures after antiretroviral initiation

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Background: Bone mineral density declines by 2–6% within 1–2 years after initiation of antiretroviral therapy (ART); however, it is uncertain whether this results in an immediate or cumulative increase in fracture rates.

Methods: We evaluated the incidence and predictors of fracture in 4640 HIV-positive participants from 26 randomized ART studies followed in the AIDS Clinical Trials Group (ACTG) Longitudinal-Linked Randomized Trial study for a median of 5 years. Fragility and nonfragility fractures were recorded prospectively at semiannual visits. Incidence was calculated as fractures/total person-years. Cox proportional hazards models evaluated effects of traditional fracture risks, HIV disease characteristics, and ART exposure on fracture incidence.

Results: Median (interquartile range) age was 39 (33, 45) years; 83% were men, 48% white, and median nadir CD4 cell count was 187 (65, 308) cells/μl. Overall, 116 fractures were reported in 106 participants with median time-to-first fracture of 2.3 years. Fracture incidence was 0.40 of 100 person-years among all participants and 0.38 of 100 person-years among 3398 participants who were ART naive at enrollment into ACTG parent studies. Among ART-naive participants, fracture rates were higher within the first 2 years after ART initiation (0.53/100 person-years) than subsequent years (0.30/100 person-years). In a multivariate analysis of ART-naive participants, increased hazard of fracture was associated with current smoking and glucocorticoid use but not with exposure to specific antiretrovirals.

Conclusion: Fracture rates were higher within the first 2 years after ART initiation, relative to subsequent years. However, continuation of ART was not associated with increasing fracture rates in these relatively young HIV-positive individuals.

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Introduction

Low bone mineral density (BMD) is a recognized metabolic complication of HIV infection and its treatment [1]. Recent studies suggest that antiretroviral therapy (ART) initiation is associated with significant short-term bone loss in the range of 2–6% over 1–2 years, irrespective of the type of ART regimen [2–8]. In contrast, longitudinal cohort studies show that BMD is either stable or increases slightly over 2 years of follow-up in younger men and women on established ART [9–11].

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It remains uncertain whether lower BMD associated with HIV infection or short-term bone loss associated with ART initiation will translate to increased fractures in younger HIV-infected (HIV-positive) individuals. Two large database studies suggest that prevalence of International Classification of Diseases, 9th Revision-coded or self-reported fractures is greater among HIV-positive individuals than in the general population [12,13], especially among older individuals [13]. Incidence of fractures has been assessed in several large cohorts of HIV-positive individuals, and compared with incidence in prospectively enrolled HIV-uninfected individuals [14], individuals within the same clinic system [15], or the general population [16,17]. Other cohorts report incidence and predictors of fracture limited to HIV-positive individuals [17–20]. These data suggest that fracture rates may be increased in HIV-positive individuals, especially those who are older [15,21] or who have other traditional risk factors for fracture [14,15,17,20,21] but may be also be associated with low CD4 cell counts at time of ART initiation [16,19]. Several studies have found an association between increased fracture rates and antiretroviral exposure [15,17,18] but most have not [14,19–23].

None of these studies specifically examined whether the acute decline in BMD with ART initiation results in an immediate increase in fracture rates. Using data from long-term follow-up of participants in the AIDS Clinical Trials Group (ACTG) studies, we determined the incidence rate and timing of fracture in relation to ART initiation as well as risk factors for incident fracture.

Methods

Study population

This was a retrospective analysis of the ACTG A5001 [ACTG Longitudinal-Linked Randomized Trial (ALLRT)] database. The ALLRT is a longitudinal cohort composed of participants prospectively randomized into 26 preselected ACTG clinical trials with specific interventions. Participants were enrolled either while participating in or shortly after completing their parent study, with long-term follow-up regardless of continued participation in the parent study and with prospective standardized data collection including physical examination and questionnaires assessing clinical and demographic information [24,25]. ALLRT includes parent studies that enrolled individuals with no ART experience prior to entry (ART naive) and those that enrolled treatment-experienced individuals (ART experienced). All ALLRT participants entered as of June 30, 2009 were included in the risk factor analysis, whereas, the analysis of timing of fracture in relation to ART initiation included the subgroup of participants from ART-naive studies only.

Baseline was defined as parent study entry. If data were not available at parent study entry, data collected at or after ALLRT entry were used instead. Baseline characteristics from parent study entry included age, sex, race/ethnicity, intravenous drug use, weight, BMI, diabetes, thyroid disease, statin use, history of AIDS-defining illness (ADI), CD4 cell count, nadir CD4 cell count, plasma HIV-1 RNA, and ART exposure by class, specific antiretroviral type, and duration of exposure based on self-reported history. Glucocorticoid use, osteoporosis diagnosis and treatment, menopause, hysterectomy, and renal insufficiency by estimated glomerular filtration rate using the modification of diet in renal disease (MDRD) calculation less than 60 ml per min or diagnosis were from ALLRT entry. Smoking, hepatitis B virus (HBV) infection by presence of HBV surface antigen or diagnosis, hepatitis C virus (HCV) infection by HCV seropositivity or diagnosis were collected after ALLRT entry (i.e. 'first available').

Fractures

In ALLRT and most parent studies, there was no specific questionnaire targeted for reporting of fracture events; therefore, fracture data were derived from self-reported adverse events. Two parent studies had questionnaires that specifically asked about fractures: A5202 ($N = 1217$) and A372 ($N = 169$). Exclusion of fractures of the face, skull, and digits was prespecified because they are generally not considered osteoporotic fractures. We excluded fractures of unknown body sites because we could not categorize them by site. All other fractures (fragility or nonfragility) were included in the analysis.

Statistical methods

The primary endpoint was the time from parent study entry date to either the first fracture event date or, if no fracture, the last ALLRT clinic visit date (censored). Cox proportional hazards models were used to investigate associations with fracture. Baseline covariates not based on parent study entry were fit as time-dependent covariates. Because there could be differences between important characteristics of the parent studies, parent study was forced into all models to control for any potential effect of parent study on the primary endpoint. Covariates that were associated with time to fracture in univariate models with $P \leq 0.10$ were examined together in a multivariate model and reduced using the backward elimination method until all remaining covariates were significant at the $P \leq 0.05$ level. Subgroups of men-only; women-only; participants who were ART-naive when randomized to the parent ACTG study; ART-naive men only, and ART-naive women only were also examined.

Incidence rate was defined as the number of participants with a new fracture divided by the total time (in person-years) at risk for new fracture, with 1 year defined as 48 weeks. Person-years were the difference between date of parent study entry to fracture date (or last ALLRT clinic visit if censored). For the ART-naive analyses,

person-years were based on the date of ART initiation. A posthoc analysis was performed in participants who were ART naive at parent study entry to investigate whether fracture incidence in the initial period after ART initiation was greater than for later periods. As these incidence rates were not from two independent populations, they could not be directly compared with a two-sample test; therefore, rates were indirectly compared using a Bayesian analysis of a piecewise exponential model fit in SAS 9.2 (SAS Institute Inc., Cary, North Carolina, USA) PROC PHREG. In this analysis, we initially fit an exponential model with one-hazard function. We next fit a piecewise exponential model based on the time of interest (2 years). This piecewise model assumed an exponential distribution in the data and fit one-hazard function for the time 0–2 years and fit a second-hazard function for the time more than 2 years. The deviance information criterion (DIC) was used to evaluate whether the two-hazard model provided a better fit than the one-hazard model. We used the calculation $\exp[(DIC_{\min} - DIC_i)/2]$, an estimate of the relative probability that the ith model minimizes the estimated information loss [26], to determine whether the two-hazard model was better than the one-hazard model. Additional cutpoints of interest (1 year, 3 and 4 years) were also examined.

Results

Participant characteristics at baseline

Of the 4640 participants, 83% were men and 48% were non-Hispanic white, with a median age of 39 years [interquartile range (IQR) = 33–45] (Table 1). The median BMI was 25 kg/m^2 (IQR = 22–28). Less than 5% had a chronic medical condition associated with fractures (osteoporosis, renal insufficiency, diabetes, thyroid disease), but 10% had documented HCV coinfection. The median nadir CD4 cell count was 187 cells/μl (IQR = 65–308; N = 4639). At baseline, 42% (1924/4636) had CD4 cell count less than 200 cells/μl, and 11% (509/4639) had HIV-1 RNA less than 500 copies/ml. At parent study entry, 3412 (74%) were ART naive. The most common ART regimens at parent study entry were NRTI-protease inhibitor or NRTI-NNRTI, with 93% of 4626 exposed to at least one NRTI, 56% to at least one protease inhibitor, and 50% to a NNRTI. Among 662 women with available data, 28% were either perimenopausal or postmenopausal.

Fractures

A total of 151 fractures occurred in 135 participants. After excluding fractures of the face, skull, digits, or unknown body sites, there were a total of 116 fractures occurring in 106 participants. The median time-to-first fracture was 2.3 years. The fracture sites included ankle/leg (N = 37), wrist/arm (31), foot (20), rib (eight), spine (six), clavicle (four), hand (four), hip (three), and pelvis (three). There were 28 fractures of the spine, hip or wrist, typical sites of major osteoporotic fractures. There were significantly fewer fractures in participants who were ART naive versus ART experienced at enrollment into parent studies during follow-up (2.0 versus 3.2%; Fisher's exact test, P = 0.02).

Fracture incidence was determined based upon time-to-first fracture from parent study entry in all participants and from ART initiation in ART-naive participants, by sex, and by whether fractures occurred at sites typical of osteoporotic fractures (Table 2). When all participants were considered, there were 106 fractures in 26 609 person-years of follow-up [incidence rate: 0.40/100 person-years; 95% confidence interval (CI) 0.33, 0.48]. When only ART-naive participants who initiated ART were considered (Fig. 1), there were 67 fractures in 17 416 person-years of follow-up (incidence rate: 0.38/100 person-years; CI: 0.30, 0.49). Considering fractures of the spine, hip, or wrist only, there were 28 fractures in 26 914 person-years in all participants (incidence rate: 0.10/100 person-years; CI: 0.07, 0.15) and 20 fractures in 17 580 person-years in ART-naive participants who initiated ART (incidence rate: 0.11/100 person-years; CI: 0.07, 0.18).

Determinants of incident fracture

In univariate analyses that included all 4640 participants, traditional risk factors for fracture (white race, history of osteoporosis, bisphosphonate use, current smoking, and glucocorticoid use) and HCV coinfection were associated with higher hazard of fracture. In contrast, immunological factors, such as CD4 cell count (baseline or nadir), baseline HIV-1 RNA, and history of ADI were not associated with hazard of fracture. In multivariate analysis, bisphosphonate use [hazard rate (HR): 11.2; 95% CI: = 1.5, 84.9; P = 0.02], HCV coinfection (HR: 2.2; 95% CI: 1.2, 4.1; P = 0.009), current smoking (HR: 1.7, 95% CI: 1.1, 2.8; P = 0.02), and glucocorticoid use (HR: 3.6; 95% CI: 1.2, 9.3; P = 0.02) remained associated with higher adjusted hazard of fracture (Table 3).

In univariate analysis restricted to 3412 participants who were ART naive at parent study entry, current smoking, glucocorticoid use, and coinfection with HCV were associated with higher hazard of fracture. CD4 cell count (baseline or nadir), HIV-1 RNA level, and duration of any antiretroviral class or specific antiretroviral were not associated with fracture. In multivariate analysis, current smoking (HR: = 1.9; 95% CI: 1.1, 3.2; P = 0.02) and glucocorticoid use (HR: 3.7; 95% CI: 1.3, 10.4; P = 0.01) remained associated with higher hazard of fracture (Table 3). When the multivariate analysis was limited to 2798 ART-naive men, current smoking (HR: 1.8; 95% CI: 1.01, 3.2; P = 0.04) and glucocorticoid use (HR: 4.8; 95% CI: = 1.7, 13.5; P = 0.003) remained associated with fracture. When the analysis was limited to

Table 1. Baseline demographic and clinical characteristics [*N* (%) or median (IQR)][a].

Demographics	Total ($N=4640$)	Fracture[b] ($N=106$)	No fracture ($N=4534$)
Age	39 (33–45)	40 (35–47)	39 (33–45)
Sex			
Male	3870 (83.4)	91 (85.9)	3779 (83.4)
Female	770 (16.6)	15 (14.2)	755 (16.7)
Race			
White	2225 (48.0)	63 (59.4)	2162 (47.7)
Black	1330 (28.7)	29 (27.4)	1301 (28.7)
Hispanic	945 (20.4)	13 (12.3)	932 (20.6)
Asian	85 (1.8)	0 (0.0)	85 (1.9)
Other/unknown	55 (1.2)	1 (0.9)	54 (1.2)
Weight (kg)	$N=4611$	$N=104$	$N=4507$
	75 (66–85)	76 (66–85)	75 (66–85)
BMI (kg/m^2)	$N=4594$	$N=104$	$N=4490$
	25 (22–28)	24 (22–28)	25 (22–28)
Smoking (first available)	$N=4616$	$N=106$	$N=4510$
	1759 (38.1)	50 (47.2)	1709 (37.9)
IVDU (ever)	441 (9.5)	13 (12.3)	428 (9.4)
Medical history			
Osteoporosis	7 (0.2)	1 (0.9)	6 (0.1)
Bisphosphonate use	10 (0.2)	1 (0.9)	9 (0.2)
Diabetes	197 (4.3)	2 (1.9)	195 (4.3)
Thyroid disease	47 (1.0)	1 (0.9)	46 (1.0)
HCV infection (history or antibody; first available)	$N=4372$	$N=80$	$N=4292$
	434 (9.9)	16 (20.0)	418 (9.7)*
HBV infection (history or HBsAg$^+$; first available)	$N=4575$	$N=70$	$N=4505$
	179 (3.9)	6 (8.6)	173 (3.8)
Renal insufficiency (diagnosis or eGFR <60 ml/min at ALLRT entry)	$N=4635$	$N=102$	$N=4533$
	138 (3.0)	5 (4.9)	133 (2.9)
Statin use	122 (2.6)	0 (0.0)	122 (2.7)
Glucocorticoid use at ALLRT entry	86 (1.9)	4 (3.8)	82 (1.8)
Perimenopausal or postmenopausal at ALLRT entry	$N=662$	$N=13$	$N=649$
	185 (27.9)	6 (46.2)	179 (27.6)
Hysterectomy at ALLRT entry	$N=709$	$N=15$	$N=694$
	102 (14.4)	5 (33.3)	97 (14.0)
HIV and ART			
History of AIDS-defining illness (ever)	937 (20.2)	25 (23.6)	912 (20.1)
CD4$^+$ cell count, nadir (cells/μl)	$N=4639$	$N=106$	$N=4533$
	187 (65–308)	177 (52–327)	187 (65–308)
CD4$^+$ cell count, baseline (cells/μl)	$N=4636$	$N=106$	$N=4530$
	242 (102–382)	234 (117–348)	242 (102–383)
CD4$^+$ cell count <200 cells/μl	$N=4636$	$N=106$	$N=4530$
	1924 (41.5)	45 (42.5)	1879 (41.5)
HIV-1 RNA ($\log_{10}$ copies/ml)	$N=4639$	$N=106$	$N=4533$
	4.6 (4.1–5.2)	4.6 (4.0–5.1)	4.6 (4.1–5.2)
HIV-1 RNA <500 copies/ml	$N=4639$	$N=106$	$N=4533$
	509 (11.0)	15 (14.2)	494 (10.9)
ART naive	3412 (73.5)[c]	67 (63.2)	3345 (73.8)*
Antiretroviral use	$N=4626$	$N=106$	$N=4520$
Nucleoside analog (NRTI) use	4305 (93.1)	97 (91.5)	4208 (93.1)
Nonnucleoside analog (NNRTI) use	2305 (49.8)	56 (52.8)	2249 (49.8)
PI use	2584 (55.8)	68 (64.2)	2516 (55.7)
Ritonavir-boosted PI use	795 (17.2)	16 (15.1)	779 (17.2)
Entry inhibitor use	79 (1.7)	1 (0.9)	78 (1.7)
ABC use	1501 (32.4)	33 (31.1)	1468 (32.5)
3TC use	2960 (64.0)	55 (51.9)	2905 (64.3)*
d4T use	754 (16.3)	21 (19.8)	733 (16.2)
TDF use	890 (19.2)	21 (19.8)	869 (19.2)
ZDV use	1891 (40.9)	32 (30.2)	1859 (41.1)*
EFV use	2212 (47.8)	52 (49.1)	2160 (47.8)

ABC, abacavir; ART, antiretroviral therapy; ALLRT, ACTG Longitudinal-Linked Randomized Trial; d4T, stavudine; EFV, efavarenz; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; IVDU, intravenous drug use; PI, protease inhibitor; 3TC, lamivudine; TDF, tenofovir; ZDV, zidovudine.

[a]Additional baseline/entry variables considered in the regression models included height, BMI classification (underweight versus not), and diagnosed weight loss/wasting. In men, hypogonadism was also examined. In women, months since last menstrual cycle, estrogen use, and selected estrogen receptor modulator (SERM) therapy use were also examined. In all analyses, univariate models containing these variables were either not significant ($P>0.10$) or did not converge due to small numbers.

[b]Excluded fractures of the face, skull, and digits.

[c]Of these, 14 participants had no antiretroviral use recorded within the short time they were under follow-up.

*P value <0.05.

Table 2. Incidence rates of first new fractures by sex and by fracture site[a].

Fractures: number and site distribution	All participants ($N=4640$)			ART naive ($N=3398$)		
	N	Fractures *N* (%)	Fractures/100 person-years (95% CI)	*N*	Fractures *N* (%)	Fractures/100 person-years (95% CI)
Total	4640	106 (2.3%)	0.40 (0.33, 0.48)	3398	67 (2.0%)	0.38 (0.30, 0.49)
Men	3870	91 (2.4%)	0.41 (0.33, 0.50)	2785	57 (2.0%)	0.40 (0.31, 0.52)
Women	770	15 (1.9%)	0.33 (0.19, 0.55)	613	10 (1.6%)	0.30 (0.14, 0.55)
Fracture sites						
Spine, hip, or wrist	4640	28 (0.6%)	0.10 (0.07, 0.15)	3398	20 (0.6%)	0.11 (0.07, 0.18)
Other	4640	78 (1.7%)	0.29 (0.23, 0.36)	3398	47 (1.4%)	0.27 (0.20, 0.36)

ART, antiretroviral therapy; CI, confidence interval.
[a]Includes only the first fracture for each person. Person-years were calculated as the difference between date of first fracture and either parent study entry in all participants analysis or ART initiation in ART-naive analysis.

614 ART-naive women, only perimenopausal or postmenopausal status (HR: 5.8; 95% CI: 1.4, 23.3; $P=0.01$) and history of hysterectomy (HR: 4.2; 95% CI: 1.2, 15.4; $P=0.03$) were associated with fracture in univariate analyses but not in multivariate analysis.

Timing of fracture in relation to antiretroviral therapy initiation

Within the first 2 years after ART initiation, 34 fractures were reported in 3398 participants followed for 6443 person-years (incidence rate: 0.53/100 person-years; 95% CI: 0.37, 0.74). In the subsequent study period, in participants with data two or more years after ART initiation, 33 fractures were reported in 2905 participants followed for 10 974 person-years (incidence rate: 0.30/100 person-years; CI: 0.21, 0.42) (Fig. 2). In a Bayesian analysis comparing piecewise exponential models of a two-hazard (with a cutpoint at 2 years) versus one-hazard function model, the DIC was lower for the two-hazard function model (877.9 versus 881.1), suggesting that the two-hazard model is three times more likely to fit the data than the one-hazard model. Similarly, we examined the DICs for two-hazard function models with cutpoints at 1, 3, and 4 years. The model with the cutpoint at 4 years had the lowest DIC (868.3); however, there were many fewer participants who contributed data after 4 years. Therefore, a two-hazard function model with a 2-year cutpoint represents the best model for these data (Fig. 2). When limited to fractures at the hip, spine, and wrist only, fracture incidence was similarly higher within the first 2 years after ART initiation than in the subsequent years.

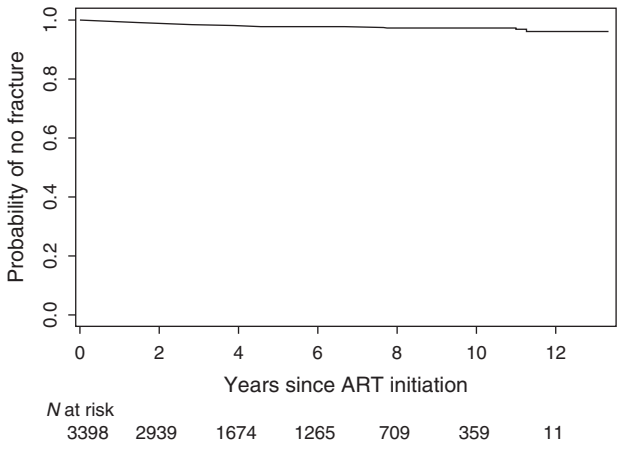

Fig. 1. Time-to-first fracture from antiretroviral therapy initiation in 3398 antiretroviral therapy-naive participants. ART, antiretroviral therapy.

Discussion

In this analysis of predominantly younger, white men starting antiretroviral regimens within randomized ACTG clinical trials, incidence of self-reported fractures was higher within the first 2 years after ART initiation than in subsequent years. Cumulative exposure to specific antiretroviral type or class, CD4 cell count, and baseline HIV-1 RNA were not associated with fractures, but traditional risk factors for fractures (current smoking, glucocorticoid use) and HCV coinfection were associated with fractures. These data suggest that the acute decline in BMD that occurs with antiretroviral initiation may be associated with clinically important changes in bone mass and quality, resulting in increased fracture risk. Alternatively, overall health status improves with ART; therefore, risk of falls and subsequent fracture may be greater early in the course of ART and decrease over time.

The overall incidence of fractures in this study was similar to rates (0.33–0.94/100 person-years) reported in other large, mixed-sex, longitudinal cohort studies of predominantly white, male HIV-infected individuals, with median ages between 36 and 50 [16,19–21]. A Danish population-based cohort study, median age 37 and 77% male, reported a slightly higher incidence rate for fractures in HIV-infected individuals of 2.1/100 person-years [17]. These rates are also similar to fracture rates of 1.2–1.8/100 person-years at all body sites reported in the general population of predominantly white residents

Table 3. Univariate and multivariate models for time to fracture.

	4640 HIV-positive participants				3398 ART-naive HIV-positive participants			
	Univariate model HR (95% CI)	*P* value	Multivariate model HR (95% CI)[a]	*P* value	Univariate model HR (95% CI)	*P* value	Multivariate model HR (95% CI)[b]	*P* value
Age (10 year)	1.02 (0.99, 1.04)	0.17			1.01 (0.98, 1.03)	0.49		
Race								
White versus others	*1.43 (0.96, 2.12)*	*0.08*			1.23 (0.76, 1.99)	0.40		
Black versus others	1.06 (0.69, 1.64)	0.79			1.09 (0.65, 1.82)	0.74		
Hispanic versus others	*0.56 (0.31, 1.00)*	*0.05*			0.69 (0.36, 1.33)	0.27		
Sex (men versus women)	1.15 (0.67, 2.00)	0.61			1.28 (0.65, 2.50)	0.48		
BMI (kg/m^2)	0.99 (0.94, 1.03)	0.48			0.97 (0.92, 1.02)	0.20		
Diabetes	0.43 (0.11, 1.76)	0.24			0.47 (0.07, 3.40)	0.46		
Renal insufficiency	1.32 (0.53, 3.30)	0.56			0.73 (0.10, 5.27)	0.75		
Osteoporosis	*7.66 (1.03, 57.1)*	*0.05*				[c]		
Bisphosphonate use	*5.41 (0.73, 40.3)*	*0.10*	*11.15 (1.46, 84.9)*	*0.02*		[c]		
HCV infection (yes versus no)	*2.68 (1.54 4.66)*	*0.0005*	*2.23 (1.23, 4.06)*	*0.009*	*2.33 (1.14, 4.78)*	*0.02*		
HBV infection (yes versus no)	*2.28 (0.98, 5.31)*	*0.06*			*2.42 (0.87, 6.73)*	*0.09*		
Smoking, time updated	*1.79 (1.17, 2.74)*	*0.008*	*1.72 (1.08, 2.75)*	*0.02*	*1.94 (1.15, 3.28)*	*0.01*	*1.92 (1.13, 3.24)*	*0.02*
IVDU (ever)	1.51 (0.84, 2.71)	0.17			1.38 (0.63, 3.02)	0.42		
Glucocorticoid use	*2.40 (0.87, 6.59)*	*0.09*	*3.63 (1.22, 9.28)*	*0.02*	*3.45 (1.23, 9.65)*	*0.02*	*3.72 (1.34, 10.37)*	*0.01*
History of AIDS-defining illness (ever)	1.11 (0.70, 1.78)	0.65			0.81 (0.41, 1.59)	0.54		
CD4, baseline (50 cells)	0.98 (0.93, 1.03)	0.42			0.97 (0.90, 1.04)	0.35		
CD4, nadir (50 cells)	0.98 (0.93, 1.04)	0.57			0.97 (0.90, 1.05)	0.45		
HIV-1 RNA ($\log_{10}$)	1.11 (0.83, 1.46)	0.49			1.17 (0.83, 1.63)	0.37		
ART experienced, baseline	1.86 (0.35, 9.94)	0.47				N/A		
Cumulative ART use (1 year)	1.01 (0.91, 1.11)	0.91			0.92 (0.62, 1.38)	0.70		
Cumulative NRTI use (1 year)	1.00 (0.91, 1.10)	0.99			0.81 (0.63, 1.05)	0.11		
Cumulative NNRTI use (1 year)	1.00 (0.89, 1.12)	0.97			1.09 (0.91, 1.31)	0.36		
Cumulative PI use (1-year)	1.04 (0.93, 1.17)	0.46			1.04 (0.86, 1.25)	0.69		
Cumulative TDF use (1 year)	1.02 (0.86, 1.22)	0.81			0.80 (0.59, 1.09)	0.16		
Cumulative ZDV use (1 year)	1.01 (0.93, 1.09)	0.88			0.97 (0.80, 1.17)	0.75		
Cumulative ABC use (1 year)	1.09 (0.97, 1.22)	0.14			1.10 (0.89, 1.37)	0.38		
Cumulative 3TC use (1 year)	1.05 (0.94, 1.17)	0.42			0.99 (0.82, 1.20)	0.92		
Cumulative D4T use (1 year)	0.93 (0.81, 1.07)	0.29			0.90 (0.68, 1.20)	0.47		
Cumulative EFV use (1 year)	1.02 (0.91, 1.14)	0.73			1.11 (0.93, 1.33)	0.26		
Cumulative RTV-PI use (1 year)	0.97 (0.82, 1.15)	0.76			0.77 (0.52, 1.13)	0.18		

The cumulative antiretroviral use variables were fit as time-updated covariates. All italicized variables listed in table were considered in the multivariate model and eliminated if they did not meet backward selection criteria of $P \leq 0.05$. Parent study was forced into model to control for any effect parent study may have had on the outcome. ABC, abacavir; ART, antiretroviral therapy; CI, confidence interval; d4T, stavudine; EFV, efavarenz; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IVDU, intravenous drug use; NRTI, nucleoside analog; NNRTI, nonnucleoside analog; PI, protease inhibitor; 3TC, lamivudine; RTV, ritonavir; TDF, tenofovir; ZDV, zidovudine.

[a]Based on 4350 participants (80 fractures) with complete data.

[b]Based on 3391 participants (67 fractures) with complete data.

[c]Did not converge.

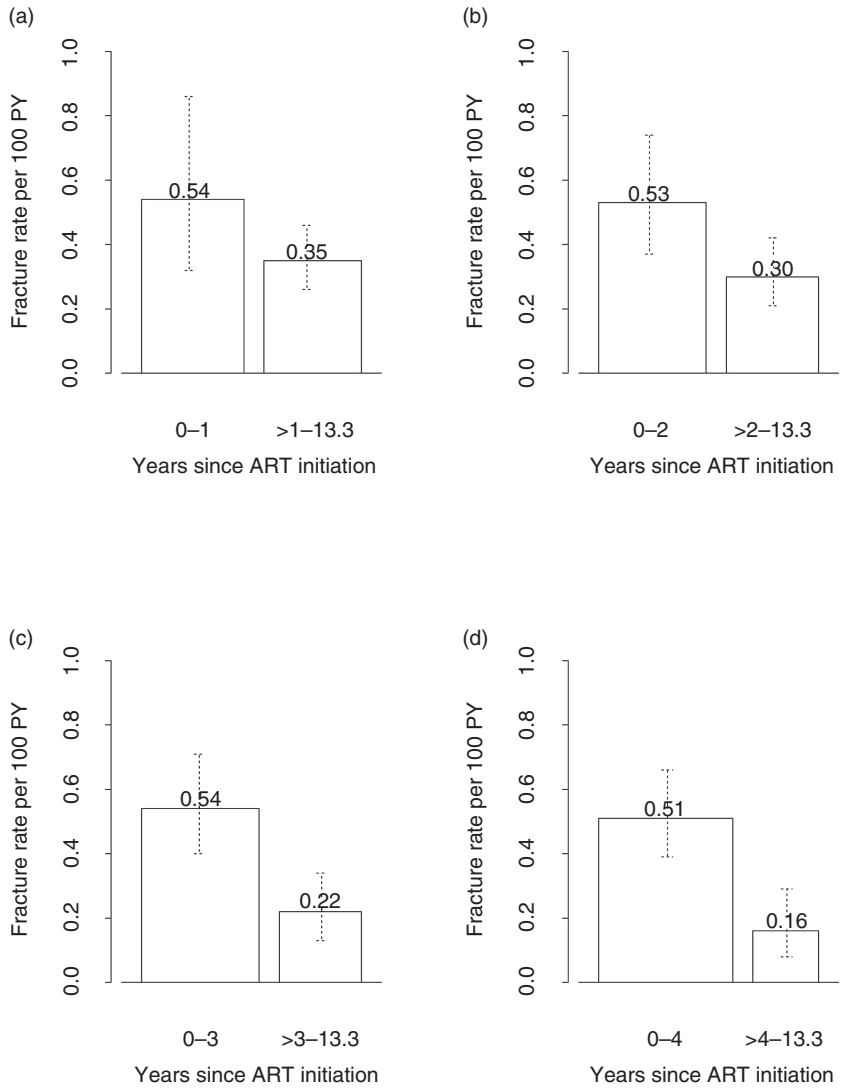

Fig. 2. Fracture incidence rates (and 95% confidence intervals) by time since antiretroviral therapy initiation in 3398 ART-naive participants. Bar widths are proportional to the number of participants. ART, antiretroviral therapy; PY, person-years.

of Minnesota in the age range of 35–39 [27]. However, fracture rates may increase disproportionately in postmenopausal HIV-infected women and older HIV-infected men, similar to available data on fracture prevalence [13].

The main predictors for fractures in HIV-positive patients from this and other studies are traditional risk factors such as smoking [14,15,17], glucocorticoid use [19], alcohol or substance abuse [19,20], low weight/BMI [15], and comorbidities such as diabetes and renal insufficiency [14–17]. Similar to our study, others have also found an association between fracture and HCV coinfection [14,16,17,20]. HCV monoinfection is associated with low bone mass [28] and increased fracture [29,30], independent of cirrhosis. The mechanisms for increased risk fracture in HCV infection are unclear but may be associated with increased alcohol use, vitamin D deficiency, hypogonadism, low BMI, increased inflammation and fall risk [28–30]. In the setting of HIV infection, Lo Re *et al.* [31] reported lower BMD in HIV/HCV coinfected than HIV monoinfected women, but higher rates of fracture in HIV-coinfected/HCV-coinfected than HIV-monoinfected or HCV-monoinfected men and women [32]. These results suggest that the negative effects of HIV and HCV on bone strength and fracture risk may be additive, and further research is warranted on the both pathogenesis and risk reduction.

Although some studies have reported an association between nadir or baseline CD4 cell count less than 200 cells/μl and fractures [19,22], the majority have found no association [14,15,17,20,21]. Hansen *et al.* [17] also found that incidence of fragility fracture was higher in

HIV-infected patients on ART, but not in ART-naive patients compared with population controls. Among HIV-infected participants, some studies found a positive association between baseline or cumulative ART and fracture incidence [15,17,18], especially with current protease inhibitor use [15] or tenofovir use [18], whereas others did not [16,19,20,23]. We found no association with exposure to ART, either by class or use of specific antiretroviral, and fracture incidence.

This is one of the first studies to examine specifically the timing of fracture in relation to ART initiation. Initiation of glucocorticoid therapy is associated with a 2–10% loss in BMD and incident vertebral fractures in 8–17% of patients within the first year [33]. Fracture risk rises sharply within the first 3–6 months after glucocorticoid initiation and then decreases after stopping, although it is uncertain whether risk returns to baseline [33]. ART initiation is somewhat analogous, although the increase in fracture risk is not nearly as pronounced. In our study, fractures occurred in only 2.0% of 3398 ART-naive participants initiating ART, which translates to an overall incidence of 0.38/100 person-years. Fracture rates were higher during the first 2 years than the subsequent years, but remain lower than after glucocorticoid initiation. Data on microarchitectural changes in bone that occur with ART initiation are lacking but may be helpful to explain why fracture rates differ between glucocorticoid and ART initiation despite similar magnitude of BMD loss. Another important factor is that the median age of participants in this study was 39 years, and that fracture risk associated with ART initiation may be much greater in older patients.

There are several strengths to our study. All participants in the ALLRT database had ART initiation as part of a randomized clinical trial; therefore, the timing of ART exposure and regimens were clearly defined in participants ART naive at entry, and any impact of confounding by treatment indication was minimized by the randomization. Additionally, standardized data reporting was utilized throughout the entire ALLRT study period.

The study also has several limitations. Certain known risk factors such as previous fracture, alcohol use, and secondary causes of osteoporosis were not available in the ALLRT or parent study databases. Most parent studies did not specify the reporting of fractures, and therefore fractures were likely underreported. In addition, it was not possible to ascertain whether a fracture was a fragility or nonfragility fracture. Study visit schedules were more intensive for the parent studies than the semiannual visits of ALLRT, especially during the first year of the parent study; therefore, the increased rate of fracture events during the first 1–4 years may be partially confounded by increased opportunity to report adverse events on the part of the participant or increased vigilance on the part of the investigator of the parent study. However, fractures are significant adverse events that participants are likely to remember and report even if the study visits were only 2–3 times per year. The incidence of other self-reported significant adverse events, such as malignancies, among ART-naive participants in the ALLRT database also decreased 2–4 years after ART initiation, but not to the extent observed with fractures. In addition, we cannot determine whether fractures early in the course of ART initiation occur as a result of decreased bone strength or because fall risk is greater earlier in the course of ART and decreases over time with improvements in overall health. Lastly, the modest size of our database limits our ability to detect significant differences in fracture rates between ART regimens, especially when restricted to the ART-naive group.

In conclusion, our data suggest that fracture risk is increased during the first few years after ART initiation, even in relatively young individuals. It is noteworthy that the increase in fracture incidence is temporally aligned with the acute 2–6% decline in BMD that has been reported in multiple studies within the first 2 years after ART initiation. Fracture incidence did not differ among the ART regimens utilized in ACTG clinical trials. Traditional risk factors for fracture such as current smoking and glucocorticoid use, and HCV coinfection were identified as important predictors of fracture that are potentially modifiable. After the initial increase, fracture rates decreased despite continuation of ART. Our results highlight a potential opportunity for preventing fractures by mitigating the bone loss associated with ART initiation. Universal recommendations to reduce fracture risk in the general population outlined by the National Osteoporosis Foundation such as adequate calcium and vitamin D intake, participation in regular weight-bearing and muscle-strengthening exercise, avoidance of tobacco, identification and treatment of alcoholism, and modification of fall risk may be especially beneficial during this period [34]. These data also provide assurance that continuation of ART is not associated with increased fractures in younger HIV-infected individuals.

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Conflicts of interest

M.T.Y has served as a consultant for Gilead and received research grants from Gilead and Bristol Myers Squibb. M.A.K., X.W., and K.T. have no conflicts of interest. M.C.H. has served as a consultant for Abbot, Bristol Myers Squibb, Roche, Merck, and Pfizer. J.S.H. has no conflicts of interest. M.A.G. has served as a consultant for Gilead, SIGA and Pfizer. H.B. has no conflicts of interest. G.A.M. has served as a scientific advisor or speaker for Bristol Myers Squibb, GlaxoSmithKline, Tibotec, and Gilead Science, has received research grants from Bristol Myers Squibb, GlaxoSmithKline, and Gilead Sciences, and is currently serving as the DSMB Chair for a Pfizer-sponsored study.

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